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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/860,844	09/29/1997	SUSAN WEININGER	GP-100C1	9470

23557 7590 05/17/2006

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/860,844	WEININGER ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,57 and 62-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28, 57, 62-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 28, 57, and 62-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must use either sequence specific polynucleotide binding constructs termed target binding assemblies (TBA) or polynucleotides encoding a TBA to treat a patient and produce a prophylactic or therapeutic result. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed method.

b) The specification provides general guidance for therapeutic or prophylactic use of TBAs in HIV infected patients on pages 38 and 56 without providing specific guidance that shows how to deliver sufficient levels of the TBA to all infected cells in the patient to eliminate an HIV infection or to eliminate symptoms of an HIV infection. The specification does not provide guidance to treat any disease other than HIV infections.

c) The specification does not provide working examples of using TBAs to produce a therapeutic or prophylactic result for any disease in any animal.

d) The nature of the invention, producing a therapeutic or prophylactic effect by gene expression regulation in a patient, is complex.

e) The prior art does not show use of TBAs to produce a therapeutic or prophylactic effect for any disease in any animal. Some embodiments of claims 63-65 read on TBAs that are antisense polynucleotides or ribozymes or multiple antisense polynucleotides. Branch reviews antisense and ribozyme technology in 1998, four year after the effective filing date of the instant application. Branch shows that antisense polynucleotides are plagued by inefficient shutdown of activity of the targeted gene product and also have numerous unpredictable side effects. Branch shows on page 48 that use of multiple antisense polynucleotides has been attempted without leading to clear strategies for therapeutic or prophylactic success. Branch concludes on page 46:

Because a single, well understood mechanism of action cannot e assumed, non-antisense effects create major difficulties for gene hunters. Years of investigation can be required to figure out what an "antisense" molecule is actually doing, as discussed further below.

Non-antisense effects also have a downside for pharmaceutical developers. Because knowledge of their underlying mechanisms is typically lacking, non-antisense effects muddy the waters. They make true antisense drugs more difficult to design and harder to commercialize. Furthermore, they can be a source of toxicity.

Claims 57, and 62-65 read on embodiments in which the TBAs comprise a restriction enzyme subunit. Chandrasegaran et al. reviews chimeric restriction enzymes in 1999, 5 years after the effective filing date of the instant application. Chandrasegaran et al. review the use of such enzymes in cultured cell systems. With regard to therapeutic or prophylactic applications, Chandrasegaran et al. summarizes the lack of progress as follows on page 847 :

The challenge, so far unfulfilled, is to develop a general means for inducing a DSB uniquely at a given locus in the genome. It appears that chimeric nucleases may meet this challenge. If this proves to be true, then the only remaining obstacle for gene therapy will be efficient delivery of the chimeric nucleases to cells in patients to stimulate correction of the defect through homologous recombination.

All claims read on TBAs that comprise a plurality of transcription factor DNA binding domains. Ansari reviews zinc finger DNA binding domains fused to transcriptional modulation domains in 2003, 8 years after the effective filing date of the instant application. Ansari shows that two recent approaches have generated libraries of zinc finger proteins with a desired sequence binding specificity. However Ansari discusses therapeutic use of zinc finger proteins as follows on page 243:

The loftier goal of using artificial transcription factors as therapeutic agents, especially in individualized therapies, faces several critical challenges. These include delivery, the need to evade an immune response, and the ability to regulate their function in response to various cellular and physiological cues. Although delivery may be achieved by retroviral means, as described by Barbas and co-workers, this method is facing intense scrutiny given recent problems with insertional mutagenesis encountered in retroviral gene therapy. The alternative, with all the attendant limitations, would be to fuse cell-penetrating peptides to protein-based artificial transcription factors. In both these respects, artificial transcription factors based on small molecules may eventually be more feasible as therapeutic agents.

Verma et al. reviews the field of gene therapy in 1997, three years after the effective filing date of the instant application. Verma summarizes the field as having no successes and shows throughout that delivery of a sufficient number of gene vectors to appropriate cells is a fundamental limitation of gene therapy techniques in 1997.

Anderson reviews the field of gene therapy in 1998, four years after the effective filing date of the instant application. Anderson shows throughout that a limitation of in vivo gene therapy is inefficient delivery to cells of the desired gene constructs. Anderson concludes on page 30:

> Gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease. Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make. It s not surprising that we have not yet has notable clinical successes. Nonetheless, the lessons we are learning in the clinic are invaluable in illuminating the problems that future research must solve.

f) The skill of those in the art of gene therapy is high.

g) The references discussed above show that it is unpredictable what methods of delivery of proteins or genes will be effective in producing the claimed therapeutic or prophylactic applications of TBAs.

h) The claims are broad in that they are drawn to use of TBAs or genes encoding TBAs to produce a therapeutic or prophylactic effect in a patient.

The skilled practitioner would first turn to the instant specification to practice the claimed invention. However the specification does not provide specific guidance or working examples of

use of TBAs or genes encoding TBAs to produce a therapeutic or prophylactic effect in a patient. As such the skilled practitioner would turn to the prior art for such guidance. However publication published years after the effective filing date of the instant application show unpredictability in use of antisense oligonucleotides and ribozymes for in vivo clinical applications, and further show a lack of success in delivering designed zinc finger proteins in in vivo clinical applications, and further show an art recognized inadequacy of vectors for use in gene therapy applications. Finally, said practitioner would turn to trial and error experimentation to practice the claimed invention. Such represents undue experimentation.

Response to Arguments

3. Applicant's arguments filed 31 March 2006 have been fully considered but they are not persuasive. The applicants provide no evidence to support their assertion that administration of a TBA is routine. It is noted that the claims require delivery of a therapeutic or prophylactic amount of TBA to be delivered to cells in vivo. The applicants state that it is not a requirement that all cells in the patient be treated, however this was not stated to be a requirement for enablement as discussed in factor b above, the rejection discusses lack of enablement for treatment of symptoms. The applicants have failed to point to any working examples of the claimed invention. The applicants have failed to point to enabling prior art in support of the enablement of the claimed invention. The applicants point to bacteriophage prior art for enablement of gene regulation by the claimed method, however the basis of the rejection is lack of enablement for the claimed therapeutic or prophylactic method of use which requires effective amounts in appropriate sites of the patient to be expressed for effective lengths of time. The bacteriophage prior art discussed by the applicants is not relevant to the issues raised in the

rejection. The applicants point to prior art experimentation on germ cell expression of therapeutic genes, however the claims are not drawn to germ cell expression, rather they are drawn to a method of therapy or prophylaxis for a patient.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

5. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. S. Brusca 8 May 2006

John S. Brusca
Primary Examiner
Art Unit 1631

jsb